September 23, 2008

Ann Tveit, Ph.D., DABT
Technical Contact
Arkema, Inc.
2000 Market Street
Philadelphia, PA 19103

Dear Dr. Tveit:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Diethylhydroxylamine, posted on the ChemRTK HPV Challenge Program Web site on February 9, 2006. I commend Arkema, Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. EPA encourages Arkema to move quickly to enhance this test plan and to complete a final package. EPA has moved energetically from the HPV Challenge Program to the Chemical Assessment and Management Program (ChAMP: www.epa.gov/champ) and is relying on Challenge chemical sponsors to provide, as expeditiously as possible, the data that are the key to this effort.

Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov. If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Diethylhydroxylamine

Summary of EPA Comments

The sponsor, Arkema Inc., submitted a test plan and robust summaries to EPA for diethylhydroxylamine (CAS No. 3710-84-7) dated December 31, 2005. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 9, 2006.

EPA has reviewed this submission and has reached the following conclusions:

1. Physical Chemical Properties. Adequate data are available for boiling point, vapor pressure, partition coefficient, and water solubility. The submitter needs to update the melting point data.

2. Environmental Fate. Adequate data are available for all endpoints.

3. Health Effects. Adequate data were submitted for the acute, genetic, repeated-dose and developmental toxicity endpoints. The submitter needs to provide data for the reproductive toxicity endpoint. The submitter also needs to address deficiencies in the robust summaries.

4. Ecological Effects. EPA agrees with the submitter's proposal to conduct studies of acute toxicity to fish and toxicity to algae. The robust summary for the invertebrate study is inadequate; the submitter needs to supply an adequate summary or provide other data for this endpoint.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on The Diethylhydroxylamine Challenge Submission

Test Plan

Physical Chemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

Adequate data are available for boiling point, vapor pressure, partition coefficient, and water solubility for the purposes of the HPV Challenge program.

Melting point. The submitter reported a value of 10 °C. EPA verified this value in the CRC and PHYSPROP database, but other data indicate a lower value. EPA found measured values of -10 °C (Beilstein On-line Search, April 18, 2006) and -8 °C (Lewis, RJ; 1996. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold p. 1283). The submitter's sources may have inadvertently changed -10 °C to 10 °C. If the submitter adds the additional values to the robust summary, the data for this endpoint will be adequate.

Environmental Fate (photodegradation, stability in water, biodegradation and fugacity)

Adequate data are available for these endpoints for the purposes of the HPV Challenge program.

Stability in water. The submitter notes that "EPIWIN was unable to calculate a hydrolysis rate". Instead, the statement should emphasize the lack of hydrolyzable functional groups.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity and reproductive/developmental toxicity)

Adequate data were submitted for the acute, repeated-dose, genetic and developmental toxicity endpoints. No data were submitted for the reproductive toxicity endpoint; however, the test plan states (section 2.1.4) that no histological lesions were noted in male or female reproductive organs in the 28-day repeated-dose inhalation study. The submitter needs to address deficiencies in the robust summaries.

Reproductive Toxicity. The test plan indicated that this endpoint was addressed by reproductive organ histology data from the 28-day repeated-dose toxicity study, but the robust summary for that study does not include data on the reproductive organs. The submitter needs to provide a robust summary of the reproductive organ data from the 28-day repeated-dose inhalation study so that the adequacy of the data can be independently assessed. However, the OECD guidelines state that for the reproductive toxicity endpoint, data from 90-day repeated-dose toxicity studies are adequate when no developmental toxicity is observed. The other data submitted for this endpoint were invalidated by the submitter because of mixed exposure to the sponsored chemical plus nitroethane (a toxicity to fertility study), mixed exposure to the sponsored chemical plus nitroethane and diethylamine hydrogen sulfite (dominant lethal study)and exposure to an impure preparation of the sponsored substance that contained its autooxidation products (dominant lethal study). Some data are also available from the invalidated carcinogenicity study in rats. EPA agrees that the use of these data is inappropriate as submitted. The *in vitro* genetic toxicity data suggest that diethylhydroxylamine has the potential to affect germ cells. Further, there is some indication from the submitted drinking water study in mice (Heicklin et al., 1984) that diethylhydroxylamine is metabolized differently in male and female mice. The array of submitted findings is inconclusive and no data were submitted on the evaluation of the reproductive organs in the 28-day repeated-dose toxicity study. Therefore, the submitter needs to provide data for the reproductive toxicity endpoint.

Developmental Toxicity. The study in rats is adequate. It is not clear why the submitter invalidated reproductive toxicity studies because of animal exposure to a mixture of substances but did not invalidate a similarly conducted developmental toxicity study in mice (Beliles et el, 1978).

Ecological Effects (fish, invertebrates, and algae)

EPA agrees with the submitter's plan to conduct studies of acute toxicity to fish and algae; OECD TGs 203 and 201, respectively, are the appropriate guidelines.

Acute Toxicity to Invertebrates. The submitted data for acute toxicity to invertebrates lack sufficient detail to evaluate study adequacy. The robust summary noted that the dissolved oxygen concentrations were >2 mg/L. For example, because the temperature was not reported, it was impossible to determine the minimum percent saturation, which could be well below the guideline requirement of ≥ 60% (see Specific Comments on the Robust Summaries, below). The submitter needs to provide adequate robust summary details, or else provide data from a study that conforms to OECD TG 202.

Specific Comments on the Robust Summaries

Physical Chemical Properties

Vapor Pressure. The summary needs to include the measurement temperature.

Health Effects

Acute Toxicity. If available, the following information needs to be added to the inhalation study: information on post-exposure observation period and statistical methods used to determine LC_{50} values, as well as data on specific sublethal effects, including respiratory distress, corneal opacity, and body weight loss.

Repeated-dose Toxicity. The following information needs to be added to the robust summary: information on the physical state of the exposure (e.g., aerosol, vapor), the full list of hematological and clinical chemistry evaluated, the full list of organs that were examined (particularly if the reproductive organs were evaluated) and the statistical methods and details of significance of effects.

Genetic Toxicity (Gene mutations). The following study details should be included in the robust summaries: individual test substance concentrations, the mean number of revertant colonies per plate for treated and control cultures as well as methods and results of determination of statistical significance.

Genetic Toxicity (Chromosomal aberrations). The following study details should be included in the robust summaries: information on criteria for scoring chromosomal aberrations, the number of cells with aberrations, and type(s) of aberrations for each treatment and positive control. In the *in vivo* study, the following information should be included: information on post-treatment time of collection of bone marrow, criteria for scoring micronucleated immature erythrocytes, properties of immature erythrocytes among total erythrocytes, numbers of micronucleated erythrocytes/animal, and mean and standard deviation of micronucleated immature erythrocytes/group.

Developmental Toxicity. The following information should be included in the robust summaries: a full list of maternal organs that were examined, tabular data concerning maternal organs and mean values of evaluated endpoints by dose level.

Ecological Effects

Invertebrates. Missing study details include GLP compliance, incorporation of analytical monitoring, number of replicates, test concentrations, test substance purity, water characteristics (pH, dissolved oxygen, temperature, alkalinity and hardness), lighting regime, number of organisms per test concentration, and statistical methods used to determine the significance of effects.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.